CLAIMS

What is claimed is:

1. A method of identifying a compound that modulates cytokine production, comprising:

a) providing an indicator composition comprising a type I polypeptide arginine methyltransferase (PRMT1) polypeptide;

b) contacting the indicator composition with a plurality of test compounds;

c) selecting from the library of test compounds a compound of interest that modulates an activity of PRMT1;

to thereby identify a compound that modulates cytokine production.

2. A method of identifying a compound that modulates T cell receptor-mediated signaling, comprising:

a) providing an indicator composition comprising a type I polypeptide arginine methyltransferase (PRMT1) polypeptide;

b) contacting the indicator composition with a plurality of test compounds;

c) selecting from the library of test compounds a compound of interest that modulates an activity of PRMT1;

to thereby identify a compound that modulates T cell receptor-mediated signaling.

3. The method of claim 1 or 2, wherein the activity of PRMT1 is a NIP45-related activity.

4. A method of identifying a compound that modulates cytokine production, comprising:

a) providing an indicator composition comprising the upstream regulatory regions controlling expression of a type I polypeptide arginine methyltransferase (PRMT1) polypeptide operably linked to a reporter gene;

b) contacting the indicator composition with a plurality of test compounds;

c) selecting from the library of test compounds a compound of interest that modulates the expression of the reporter gene;

to thereby identify a compound that modulates cytokine production.

5. The method of claim 4, further comprising determining the effect of the compound of interest on a NIP45-related activity of PRMT1.

6. The method of claim 1 or 2, wherein the indicator composition is a cell that expresses the PRMT1 polypeptide.

7. The method of claim 6, wherein the cell has been engineered to express the PRMT1 polypeptide by introducing into the cell an expression vector encoding the PRMT1 polypeptide.

8. The method of claim 1 or 2, wherein the indicator composition is a cell free composition.

9. The method of claim 1 or 2, wherein the step of determining the effect of the compound of interest on an activity of PRMT1 comprises measuring the ability of the PRMT1 to methylate one or more arginine residues of a target polypeptide.

10. The method of claim 9, wherein the target polypeptide is NIP45.

11. The method of claim 6, wherein the cell further comprises a NIP45 polypeptide.

12. The method of claim 6, wherein the cell further comprises an NFAT polypeptide.

13. The method of claim 3, wherein the step of determining the effect of the compound of interest on a NIP45-related activity of PRMT1 comprises measuring cytokine production or cytokine gene transcription.

14. The method of claim 13, wherein the cytokine is IFN-γ or IL-4.

15. A method for identifying a compound that modulates cytokine production in a non-T cell, comprising;

a) providing non-T cell comprising a NIP45 molecule;

b) contacting the non-T cell with a plurality of test compounds; and

c) selecting from the library of test compounds a compound of interest that modulates the activity of NIP45;

to thereby identify a compound that modulates cytokine production in a non-T cell.

16. The method of claim 15, wherein the cell further comprises PRMT1.

17. The method of claim 15, wherein the cell further comprises NFAT.

18. The method of claim 15, wherein the activity of NIP45 is selected from the group consisting of: binding to NFAT, binding to PRMT1, and activation of gene transcription.

19. The method of claim 18, wherein the gene is selected from the group consisting of: IL-4, IFN-γ, Egr2, Egr3, c-Rel, and p65.

20. A method for identifying a compound that modulates gene expression comprising:

a) contacting an indicator composition comprising a first polypeptide comprising amino acids 1-32 of NIP45 and a second polypeptide which is a PRMT1 polypeptide with a plurality of test compounds;

b) detecting an activity of the first polypeptide or a NIP45-related activity of the second polypeptide in the presence and absence of a test compound, and

c) selecting a compound of interest that modulates an activity of the first or second polypeptide;

to thereby identify a compound that modulates gene expression.

21. The method of claim 20, wherein the indicator composition is a cell.

22. The method of claim 20, wherein the cell further comprises an NFAT polypeptide and the activity of the first polypeptide is detected by measuring the binding of the first polypeptide to the NFAT polypeptide.

23. The method of claim 22, wherein the NFAT polypeptide is selected from the group consisting of: NFATc1, NFATc2, and NFATc3.

24. The method of claim 20, wherein the activity of the first polypeptide is detected by measuring transcription from a promoter.

25. The method of claim 24, wherein the promoter is an IL-4 or IFN-γ promoter.

26. The method of claim 24, wherein the promoter is selected from the group consisting of: the Egr2, Egr3, c-Rel, and p65 promoter.

27. The method of claim 20, wherein the indicator composition is present in a cell free system.

28. The method of claim 20, wherein the NIP45-related activity of the second polypeptide is detected by measuring the methylation of one or more arginine residues of NIP45.

29. The method of claim 20, wherein the NIP45-related activity of the second polypeptide is detected by measuring the interaction between the second polypeptide and the first polypeptide.

30. The method of claim 20, wherein the test compounds are present in a library of small molecules.

31. The method of claim 28, wherein the test compound decreases the degree of arginine methylation of NIP45 as compared to the degree of arginine methylation of NIP45 in the absence of the test compound, and the test compound is identified as an agent that reduces cytokine production.

32. The method of claim 28, wherein the test compound increases the degree of arginine methylation of NIP45 as compared to the degree of arginine methylation of NIP45 in the absence of the test compound, and the test compound is identified as an agent that increases cytokine production.

33. A method for identifying a compound that modulates an interaction between NIP45 and a PRMT polypeptide, comprising:

a) contacting an indicator composition comprising a polypeptide comprising amino acids 1-32 of NIP45 and a PRMT polypeptide with a plurality of test compounds;

b) detecting a readout of the interaction between the NIP45 and PRMT polypeptides in the presence and absence of a test compound, and

c) selecting a compound of interest that modulates the interaction between the NIP45 and PRMT polypeptides;

to thereby identify a compound that modulates an interaction between NIP45 and PRMT polypeptide.

34. The method of claim 33, wherein the indicator composition is a cell based composition.

35. The method of claim 33, wherein the indicator composition is a cell free composition.

36. The method of claim 33 wherein the readout of the interaction between the NIP45 and PRMT1 polypeptides is the binding of NIP45 to PRMT1 or the methylation of one or more arginine residues of NIP45.

37. The method of claim 33, wherein the readout of the interaction between the first and second polypeptides is modulation of gene transcription.

38. The method of claim 37, wherein the gene is selected from the group consisting of IL-4 and IFN-γ.

39. The method of claim 33, wherein said test compounds are present in a library of small molecules.

40. The method of claim 33, wherein the test compound decreases the interaction between NIP45 and PRMT1 as compared to the interaction between NIP45 and PRMT1in the absence of the test compound, and the test compound is identified as an agent that reduces interaction between NIP45 and PRMT1.

41. The method of claim 33, wherein the test compound increases the interaction between NIP45 and PRMT1 as compared to the interaction between NIP45 and PRMT1 in the absence of the test compound, and the test compound is identified as an agent that increases interaction between NIP45 and PRMT1.

42. A method for identifying a compound that modulates cytokine production in a cell, comprising;

a) providing a cell containing one or more constructs which comprise: a cytokine promoter operably linked to a reporter gene, a nucleotide sequence encoding

PRMT1, and a nucleotide sequence encoding at least one activator of cytokine gene transcription;

b) stimulating the cell with an activating signal;

c) contacting the cell with a plurality of test compounds;

d) measuring the expression or activity of the reporter gene; and

e) selecting a compound of interest that modulates the expression or activity of the reporter gene,

to thereby identify a compound that modulates cytokine production in a cell.

43. The method of claim 42, wherein the cytokine promoter is an IFNγ promoter.

44. The method of claim 42, wherein the activator of cytokine gene transcription is T-bet.

45. The method of claim 42, wherein the cytokine promoter is an IL-4 promoter.

46. The method of claim 42, wherein the activator of cytokine gene transcription is selected from the group consisting of NFATc2 and NIP45.

47. The method of claim 42, wherein the cell further comprises a construct comprising a nucleotide sequence encoding c-maf.

48. A method for modulating cytokine production in a non-T cell comprising contacting a non-T cell with an agent that modulates the expression and/or activity of at least one molecule selected from the group consisting of: NIP45, PRMT1, and NFAT, such that cytokine production in the non-T cell is modulated.

49. The method of claim 48, wherein the cell is selected from the group consisting of: a dendritic cell, an NK cell, and a mast cell.

50. A method for modulating cytokine production comprising contacting a T cell with an agent that modulates PRMT1 expression and/or activity such that cytokine production is modulated.

51. The method of claim 50, wherein the T cell is a $CD4^+$ T cell.

52. The method of claim 50, wherein the T cell is a $CD8^+$ T cell.

53. The method of claim 48 or 50, wherein IFNγ production is modulated.

54. The method of claim 48 or 50, wherein IL-4 production is modulated.

55. The method of claim 48 or 50, wherein PRMT1 activity is increased, thereby increasing cytokine production.

56. The method of claim 48 or 50, wherein PRMT1 activity is decreased, thereby decreasing cytokine production.

57. A method for modulating IFNγ production, comprising contacting a cell with an agent that modulates PRMT1 expression and/or activity such that IFNγ production is modulated.

58. The method of claim 56, wherein the cell is an NK cell or a dendritic cell.

59. A method for modulating IL-4, comprising contacting a cell with an agent that modulates PRMT1 expression and/or activity such that IL-4 production is modulated.

60. The method of claim 58, wherein the cell is an NK cell or a mast cell.

61. A method for modulating the relative number of Th1 or Th2 cells in a population of T cells, comprising contacting the population of T cells with an agent that modulates PRMT1 activity such that the relative number of Th1 or Th2 cells in the population is modulated.

62. A method of treating a subject that would benefit from the modulation of cytokine production comprising contacting an immune cell from the subject with an agent that modulates PRMT1 expression and/or activity in the immune

cell such that cytokine production is modulated and the subject that would benefit from the modulation of cytokine production is treated.

63. The method of claim 61, wherein PRMT1 activity is increased, thereby increasing cytokine production.

64. The method of claim 63, wherein the patient is suffering from an immunodeficiency.

65. The method of claim 61, wherein PRMT1 activity is decreased, thereby decreasing cytokine production.

66. The method of claim 65, wherein the subject is suffering from an autoimmune or allergic condition.